

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 0 963 980 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
05.06.2002 Bulletin 2002/23

(51) Int Cl.7: **C07D 253/06**, G01N 30/00,
G01N 30/22, G01N 30/36,
G01N 30/90, G01N 33/15

(21) Application number: 99200695.7

(22) Date of filing: 10.03.1999

(54) **1,2,4-Triazine derivative, its preparation and its use as reference marker for testing purity and stability of "lamotrigine"**

1,2,4-Triazin Derivat, dessen Herstellung und dessen Verwendung als Referenzmarker um die Reinheit und Stabilität von "Lamotrigin" zu bestimmen

Dérivé de 1,2,4-triazine, la preparation et l'utilisation comme marqueur de référence pour vérifier la pureté et la stabilité de "lamotrigine"

(84) Designated Contracting States:
**AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC
NL PT SE**
Designated Extension States:
AL LT LV RO SI

(74) Representative: **Stott, Michael John et al**
GlaxoSmithKline
Corporate Intellectual Property (CN9.25.1)
980 Great West Road
Brentford, Middlesex TW8 9GS (GB)

(30) Priority: 10.06.1998 GB 9812413

(56) References cited:
WO-A-96/20934

(43) Date of publication of application:
15.12.1999 Bulletin 1999/50

(60) Divisional application:
01203376.7 / 1 170 588

(73) Proprietor: **THE WELLCOME FOUNDATION
LIMITED**
Greenford, Middlesex UB6 0NN (GB)

(72) Inventors:
• **Edmeades, Lorraine Mary**
Stevenage, Herts. SG1 2NY (GB)
• **Griffith-Skinner, Nigel Arthur**
Dartford, Kent DA1 5AH (GB)
• **Hill, Derek Anthony**
Sittingbourne, Kent ME9 7RL (GB)
• **Hill, Graham Thornton**
Ware, Herts. SG12 ODP (GB)
• **Packham, Terrence William**
Dartford, Kent DA1 5AH (GB)

- **SAILSTAD J.M. & FINDLAY J.W.A.:**
"Immunofluorometric assay for lamotrigine
(Lamictal) in human plasma" THERAPEUTIC
DRUG MONITORING, US, RAVEN PRESS, NEW
YORK, NY, vol. 13, no. 5, September 1991
(1991-09), pages 433-442, XP000882274
- **LONDERO D. & LO GRECO P.:** "New
micromethod for the determination of
lamotrigine in human plasma by
high-performance liquid chromatography"
JOURNAL OF CHROMATOGRAPHY B:
BIOMEDICAL SCIENCES & APPLICATIONS, NL,
ELSEVIER SCIENCE PUBLISHERS, vol. 691, no.
1, 28 March 1997 (1997-03-28), pages 139-144,
XP004059330 ISSN: 0378-4347
- **DASGUPTA A. & HART A.P.:** "Lamotrigine
analysis in plasma by gas
chromatography-mass spectrometry after
conversion to a tert.-butyldimethylsilyl
derivative" **JOURNAL OF CHROMATOGRAPHY**
B: BIOMEDICAL SCIENCES & APPLICATIONS,
NL, ELSEVIER SCIENCE PUBLISHERS, vol. 693,
no. 1, 23 May 1997 (1997-05-23), pages 101-107,
XP004068519 ISSN: 0378-4347

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 0 963 980 B1

Description

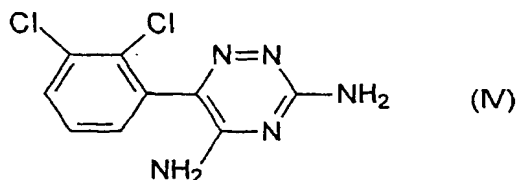
[0001] The present invention relates to compounds useful as reference markers for the analysis of lamotrigine and pharmaceutical formulations thereof.

[0002] In order to secure marketing approval for a new drug product, a drugs manufacturer must submit detailed evidence to the appropriate regulatory authority to show that the product is suitable for release on to the market. The regulatory authority must be satisfied, *inter alia*, that the active agent is acceptable for administration to humans and that the particular formulation which is to be marketed is free from impurities at the time of release and has an appropriate shelf-life.

[0003] Submissions made to regulatory authorities therefore typically include analytical data which demonstrate (a) that impurities are absent from the drug at the time of manufacture, or are present only at a negligible level, and (b) that the storage stability, i.e. shelf-life, of the drug is acceptable. These data are usually obtained by testing the drug against an external standard, or reference marker, which is a suitably pure sample of a potential impurity or a potential degradation product.

[0004] Potential impurities in pharmaceutically active agents and formulations containing them include residual amounts of synthetic precursors to the active agent, by-products which arise during synthesis of the active agent, residual solvent, isomers of the active agent, contaminants which were present in materials used in the synthesis of the active agent or in the preparation of the pharmaceutical formulation, and unidentified adventitious substances. Other impurities which may appear on storage include substances resulting from degradation of the active agent, for instance by oxidation or hydrolysis.

[0005] Lamotrigine is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, of formula (IV)



[0006] It is a known compound which is useful in the treatment of disorders of the central nervous system (CNS), in particular epilepsy, as described for example in EP-A-0021121. Both lamotrigine *per se* and its pharmaceutical formulations are manufactured relatively free from impurities. In particular, lamotrigine remains stable during the manufacture of its pharmaceutical formulations.

[0007] Sailstad J.M. & Findlay J.W.A. Therapeutic Drug Monitoring, US, Raven Press, New York, NY, vol 13, no. 5 Sept 1991, pages 433-442 describes an immunofluorometric assay for lamotrigine and analogs including 123W79 (compound A).

[0008] WO96/20934 describes a new process for preparing lamotrigine and discloses that under certain circumstances a side reaction which competes with the new lamotrigine manufacturing process may occur and that this side reaction results in the formation of 3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine-5-(4H)-one (compound A).

[0009] Londero D. & Lo Greco P.J. Chromatog. B: Biomedical Sciences & Applications, NL, Elsevier Science Publishers, vol 691, no. 1, 28 March 1997, pages 139-144 describes a method for assaying blood plasma for the presence of lamotrigine using HPLC and requires the use of an internal standard 3,5-diamino-6-(2-methoxyphenyl)-1,2,4-triazine.

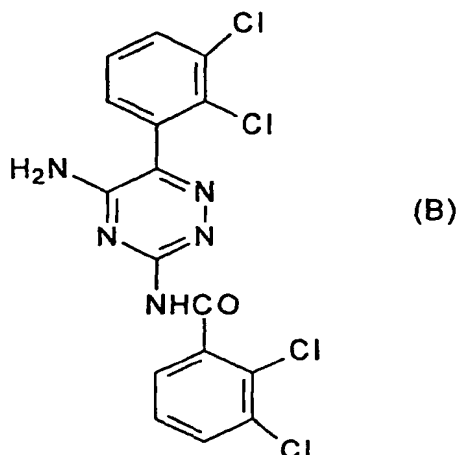
[0010] Dasgupta A. & Hart A.P.J. Chromatog B: Biomedical Sciences & Applications, NL, Elsevier Science Publishers, vol 693, no. 1, 23 May 1997, pages 101-107 also describes a method for assaying blood plasma for the presence of lamotrigine where the lamotrigine is derivatised with N-methyl-N-(tert-butyldimethylsilyl) trifluoroacetamide before undergoing gas chromatographic-mass spectral analysis.

[0011] It has now been appreciated that two compounds can be used as reference markers for the analysis of lamotrigine or of pharmaceutical dosage forms comprising lamotrigine. One of the compounds is a potential degradation product of lamotrigine and the other is a potential contaminant arising from side reactions during the synthesis of lamotrigine.

[0012] The present invention therefore provides a method of testing the purity of a sample of lamotrigine or a pharmaceutical dosage form comprising lamotrigine, which method comprises assaying the said sample for the presence of N-[5-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine-3-yl]-2,3-dichlorobenzamide. In the method of the invention the said compound is acting as a reference marker.

[0013] The compound used as a reference marker is novel. The invention therefore provides a compound which is

N-[5-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine-3-yl]-2,3-dichlorobenzamide of formula B:

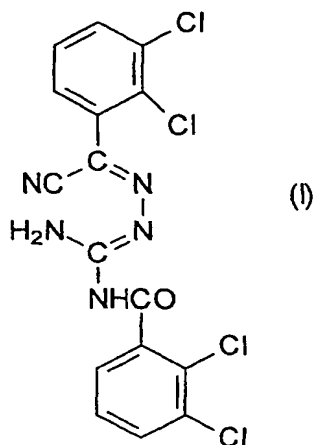


[0014] The compound of formula B (compound B) may be produced directly by treating lamotrigine with 2,3-dichlorobenzoyl chloride in pyridine. However, it has utility as a reference marker for lamotrigine because it is a potential contaminant arising from side reactions which can occur during the synthesis of the drug. In practice the level of this contaminant is controlled at a maximum of 0.5% in the crude lamotrigine by thin-layer chromatography (TLC). Recrystallisation of crude drug of this quality then results in the production of lamotrigine meeting the required purity level for commercial production of not more than 2% total impurities.

[0015] The synthesis of lamotrigine is illustrated in Reference Example 1. 2,3-Dichlorobenzoyl cyanide, which is intermediate 1.4 in that synthesis, may contain up to 10% of 2,3-dichlorobenzoic anhydride as a contaminant. When the 2,3-dichlorobenzoyl cyanide is treated with a solution of aminoguanidine bicarbonate in sulphuric acid, which is step (d) in Reference Example 1, the adduct (Z)-2-(2,3-dichlorophenyl)-2-(guanidinoimino)acetonitrile (intermediate 1.5) is produced. The anhydride contaminant can then react with the latter adduct to form (Z)-2-(2,3-dichlorophenyl)-2-[N'-(2,3-dichlorobenzoyl)guanidinoimino]acetonitrile, which is the direct precursor to compound B. Cyclisation of the precursor in propan-1-ol under reflux yields compound B.

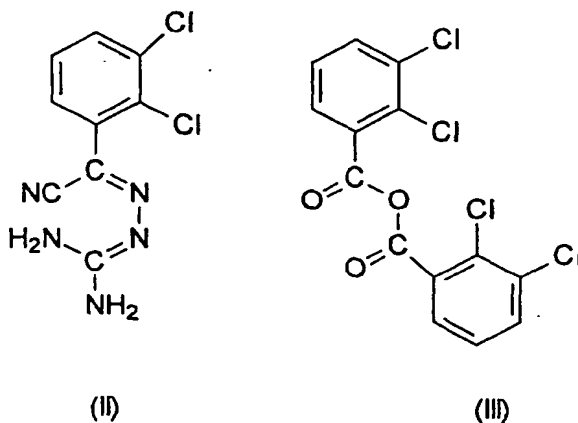
[0016] The present invention therefore further provides a process for producing compound B, which process comprises

- (i) reacting 2 equivalents of 2,3-dichlorobenzoyl chloride with 1 equivalent of lamotrigine dissolved in pyridine at a temperature of less than 35°C; or
- (ii) cyclising a compound of formula (I):



20 in propan-1-ol under reflux.

[0017] In step (ii), the compound of formula (I) is produced by reacting together compounds of formulae (II) and (III):



in the presence of a mineral acid, for instance sulphuric acid.

[0018] The compound of formula (II) is produced by treatment of 2,3-dichlorobenzoyl cyanide with a solution of amino-guanidine bicarbonate in sulphuric acid.

[0019] When compound B is used as a reference marker it must be in a suitably pure form. Compound B produced as described above may be purified if necessary to achieve the desired purity level. The process of the invention for producing compound B as described above may therefore include the additional step of purifying the resulting compound.

[0020] Purification may be carried out by conventional methods which are routine in organic synthesis. For instance, the compound may be heated in an organic solvent such as a C₁-C₆ alkanol, filtered and dried under vacuum. Heating is typically carried out at the reflux temperature of the solvent. A C₁-C₆ alkanol is preferably propanol. Alternatively the compound may be recrystallised from a hot C₁-C₆ alkanol solvent, preferably hot propanol.

[0021] Compound B is preferably finally recovered in substantially pure form. The purity level of a final sample of either compound is typically at least 80%, for example at least 85%, more preferably at least 90%. Purity levels above 90% may be desirable but are not essential. The purity level may be, for instance, at least 92%, at least 95% or at least 98%. Even more desirably the purity level is 99% or 99.5%.

[0022] Either lamotrigine itself (also referred to as drug substance) or a pharmaceutical dosage form comprising

lamotrigine (also referred to as drug product) may be analysed for purity or stability to degradation. For instance, it is necessary to ensure that lamotrigine is pure following its manufacture. The drug substance is therefore typically assayed for the process impurity (compound B). Pharmaceutical dosage forms of lamotrigine need to be analysed to check that the active agent remains stable to degradation both during manufacture of the drug product and after several years' storage.

[0023] The test sample of drug substance or drug product to be analysed may be assayed by one or more conventional analytical techniques. The analytical techniques include high performance liquid chromatography (HPLC) and thin layer chromatography (TLC). The results obtained are compared with the results obtained from testing a substantially pure reference sample of compound B. The content of the or each compound in the test sample can then be determined.

[0024] In one aspect, the method of the invention is for testing the purity of a sample of lamotrigine, and includes the steps of:

- (i) dissolving a sample of lamotrigine in a solvent to produce a sample solution;
- (ii) dissolving a sample of 3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine-5-(4H)-one or N-(5-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine-3-yl)-2,3-dichlorobenzamide in a solvent to produce a reference marker standard solution;
- (iii) subjecting the sample solution and the standard solution to thin layer chromatography to obtain a TLC chromatogram for each; and
- (iv) estimating the intensity of any secondary spot obtained in the chromatogram of the sample solution, which corresponds in R_f value to the reference marker, against the spot due to the reference marker in the chromatogram of the standard solution.

[0025] The invention also provides the use of N-[5-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine-3-yl]-2,3-dichlorobenzamide as a reference marker in analysing the purity of a sample of lamotrigine or a sample of a pharmaceutical dosage form comprising lamotrigine.

[0026] In practice lamotrigine is relatively pure and is quite stable on storage. Analytical testing of the drug substance itself, or of pharmaceutical dosage forms containing lamotrigine, therefore serves principally to confirm that compounds A and/or B are absent or are present only at levels below the limit of detection for the analytical technique in question (about 0.3% w/w for TLC and 0.06% w/w for HPLC).

[0027] As an alternative to assaying a sample of the reference marker separately each time it is desired to assess data obtained from analysing a sample of drug substance or drug product, a parameter known as the Response factor (R) may instead be used. A Response factor is a previously determined ratio of a numerical result obtained by testing a sample of compound B using a given analytical technique, to the corresponding numerical result obtained by testing pure lamotrigine at an equivalent concentration. The numerical result in question may be, for instance, an HPLC peak area response value. Thus, given appropriate analytical results for pure lamotrigine and for a test sample of a pharmaceutical dosage form of lamotrigine, the known Response factor for compound B can be used to calculate the amount of that particular reference marker in the test sample.

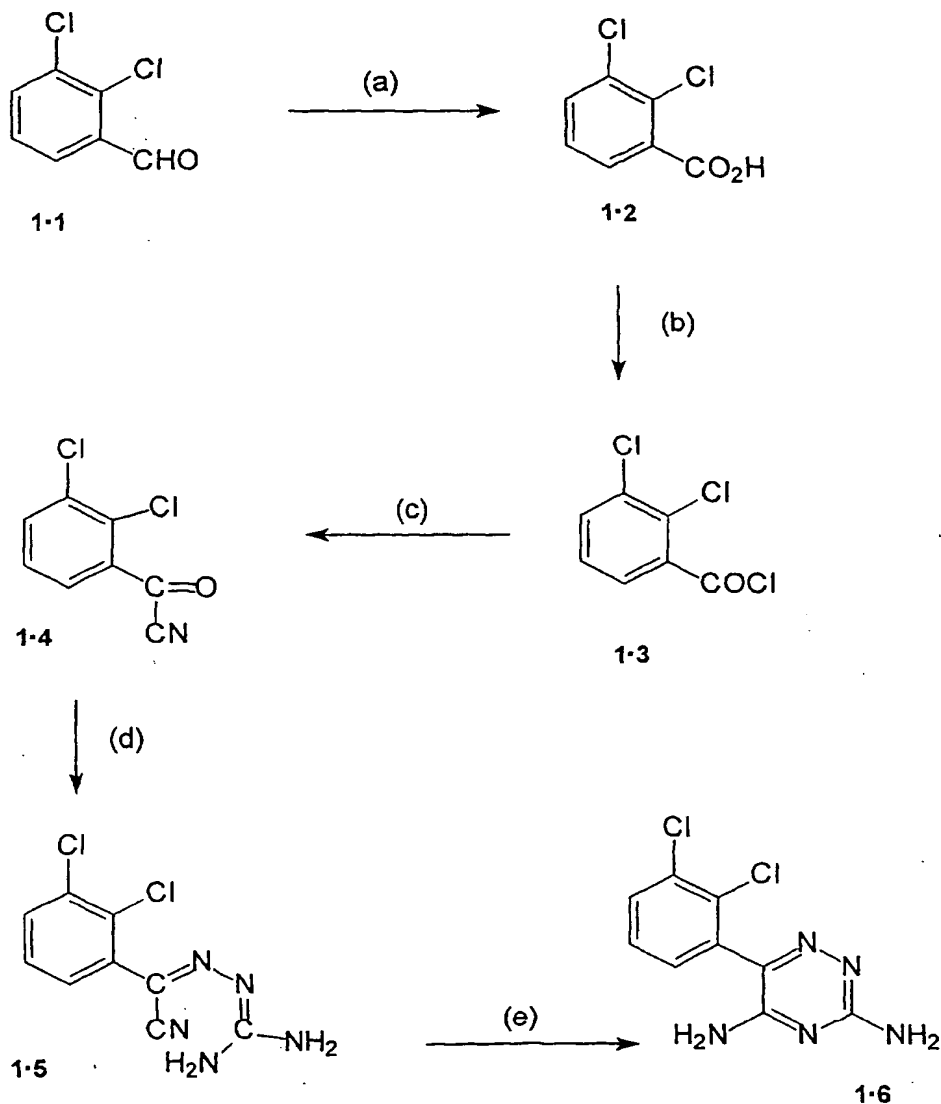
[0028] The calculation may be illustrated with reference to HPLC analysis results as follows:

$$\% \text{ w/w of compound A or B in test sample relative to lamotrigine} = \frac{A_r \times W_s}{A_s \times R}$$

wherein:

- A_r = main peak area of the compound in HPLC test solution
- A_s = main peak area of lamotrigine alone in HPLC standard solution
- R = Response factor of the compound
- W_s = weight (in mg) of the standard taken

[0029] The invention will be further described in the Examples which follow.

Reference Example 1: Preparation of lamotrigine**Step a: Preparation of 1.2**

[0030] A solution of 1.1 (1 mole), tertiary-butyl alcohol, water and sodium hydroxide (2 moles) was stirred and hydrogen peroxide solution (35% w/w, 4 moles) was added at 50-60°C over 3 hours. After stirring at 55-60°C for 30 minutes, the tertiary-butyl alcohol was removed by distillation and the aqueous solution was washed with toluene. The aqueous solution was acidified to pH 1-2, and the product was filtered and washed with water. The damp solid was either used directly in the next stage of the process or dried at 80-90°C to afford a white solid in 75% yield.

Steps (b) and (c): Preparation of 1.4

[0031] A solution of 1.2 (1 mole) in toluene was stirred and dried by distillation. It was then cooled and pyridine (0.005

moles) was added, followed by a slow addition of thionyl chloride (1.1 moles). The solution was heated under reflux for 1 hour, then concentrated *in vacuo* to afford crude 1.3. Potassium iodide (1.2 moles) was added, followed by cuprous cyanide (1.2 moles) and any remaining solvent was removed by distillation until the internal temperature was 140-144°C. This temperature was maintained for 18-24 hours, then the reaction mixture was cooled, diluted with toluene and filtered to remove inorganic salts. The solution was evaporated to dryness *in vacuo* at 60-70°C, and the residual oil crystallised from petroleum ether to yield 1.4 as a yellow solid in 77% yield.

Step d: Preparation of 1.5

[0032] Aminoguanidine bicarbonate (1.75 moles) was dissolved in 9.3-10.0 M sulphuric acid solution. A solution of 2,3-dichlorobenzoyl cyanide (1 mole) in acetonitrile was added and the suspension stirred at 20-30°C for 42-48 hours. The crude product was filtered and washed with water. The solid was added to sodium hydroxide solution below 35°C, then the product was filtered, washed with water and dried at 80-90°C to obtain 1.5 as a yellow solid in 66% yield.

Step (e) Preparation of Crude Lamotrigine

[0033] A solution of 1.5 in propan-1-ol was stirred under reflux for 90-120 minutes, cooled to 15-25°C and crude lamotrigine was filtered to obtain a pale brown solid in a 90% yield (on a dry basis). The crude lamotrigine was purified by recrystallisation from propan-1-ol, using charcoal, and cooling the solution to 15-25°C. The solid was filtered, washed with propan-1-ol and dried at 80-90°C to afford pure lamotrigine.

Example 2: Preparation of N-[5-Amino-6-(2,3-dichlorophenyl)-1,2,4-triazine-3-yl]-2,3-dichlorobenzamide (Compound B)

[0034] Lamotrigine (512.00g, 2.00 moles) was dissolved in pyridine (3 l) and 2,3-dichlorobenzoyl chloride (873.00g, 96% pure, equivalent to 838.10g, 4.00 moles) was added below 35°C with stirring under anhydrous conditions. The acid chloride was added in two equal portions. The second portion of acid chloride was added after 30 minutes from the start of the reaction and stirred below 35°C for a further 30 minutes.

[0035] The resulting mixture was concentrated to almost dryness and then triturated with chloroform (1300 ml) for 10 minutes with stirring. The resulting solid was filtered and washed with chloroform (3 x 50 ml) and dried at room temperature to a weight of 308g, 36% (based on compound B). A sample of the crude product (50.0g) was heated with methanol (500 ml) at reflux temperature with stirring for 1 hour and the resulting hot mixture was filtered to afford compound B in very pure form (37.0g).

[0036] The product has the following physical characteristics:

Molecular formula: $C_{16}H_9Cl_4N_5O$ Molecular mass: 429.09

Infra-red (KCl): ν_{max} (cm^{-1}): 3468, 3300, 3202,

3385, 3277, 1687,

1625, 1559, 1414,

1387, 1538, 1459,

1253, 1157, 1136,

1116, 790, 775,

741, 724

1H nmr: δ/ppm in d_6 -dmso (39 mg ml^{-1})/300 MHz:

10.85 (1H, bs); 7.8 (1H, bs); 7.1 (1H, bs);

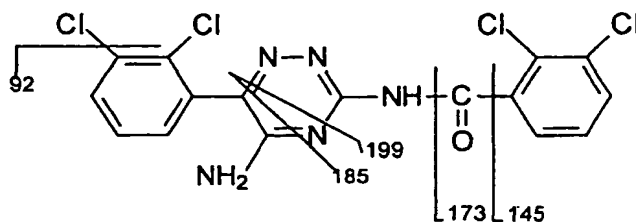
7.77 (1H, d, $J=7Hz$); 7.73 (1H, d, $J=7Hz$); 7.5 (4H, m); 4.08(bs); 3.32 (bs, water); 3.18 (s); 2.50 (quintet, $dmso-d_6$); 2.31 (s, methane sulphonate); 0.00 (s, TMS).

Mass spectroscopy

[0037]

Chemical ionisation (CI): m/z : 428 ($M+1$)⁺; 430, 432 and 434 (associated isotope ions).

Electron impact (EI): m/z : 428 ($m+1$)⁺; 392, 199, 185, 173, 145 (fragment ions as indicated below:)



Example 4: Determination of Compound B in drug substance (lamotrigine, 25µm particle size) by TLC

Test 1 - compound B

[0038] The following standard and test solutions were prepared in an equivolume mixture of methanol and 2-methoxyethanol:

- solution 1: 5.0% w/v solution of the sample
- solution 2: 5.0% w/v solution of lamotrigine reference sample
- solution 3: 0.02% w/v solution of compound B
- solution 4: 1.0 ml of solution 2 diluted to 250 ml
- solution 5: 10.0 ml of solution 4 diluted with 10.0 ml of solution 3
- solution 6: 7.5 ml of solution 5 diluted to 10.0 ml
- solution 7: 5.0 ml of solution 5 diluted to 10.0 ml
- solution 8: 2.5 ml of solution 5 diluted to 10.0 ml

[0039] The following TLC operating conditions were used:

- plate: 20x20 cm plate coated with a 0.25 mm layer of Silica gel 60 F₂₅₄
- mobile phase: ethyl acetate/glacial acetic acid/methanol (85:10:5 v/v)
- spot loading: 10µl of each solution
- length of run: 10 cm

[0040] The TLC plate was allowed to dry in air and was then viewed under ultraviolet light at 254 nm. The test was not valid unless the chromatogram obtained with solution 5 exhibited two clearly separated spots and the corresponding spots in the chromatogram from solution 8 were both detectable.

[0041] The intensity of any secondary spot corresponding in R_f value to compound B obtained in the chromatogram of solution 1 against the spots due to compound B obtained in the chromatograms of solutions 5, 6, 7 and 8 (equivalent to 0.2, 0.15, 0.1 and 0.05% w/w, respectively) was estimated.

[0042] The intensity of any secondary spots obtained in the chromatogram of solution 1 against the spots due to lamotrigine obtained in the chromatograms of solutions 5, 6, 7 and 8 (equivalent to 0.2, 0.15, 0.1 and 0.05%, respectively) were estimated.

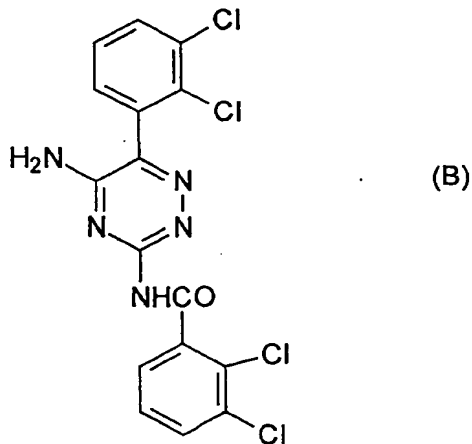
The R_f values obtained were: lamotrigine: 0.20
compound B: 0.60

[0043] Throughout this specification and the appended claims it is to be understood that the words "comprise" and "include" and variations such as "comprises", "comprising", "includes", "including" are to be interpreted inclusively, unless the context requires otherwise. That is, the use of these words may imply the inclusion of an element or elements not specifically recited.

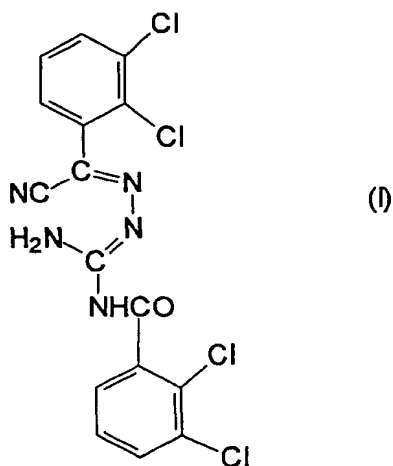
[0044] The present invention has been described by way of example only, and it is to be recognised that modifications thereto which fall within the scope and spirit of the appended claims, and which would be obvious to a skilled person based upon the disclosure herein, are also considered to be included within the invention.

Claims

1. A compound which is N-[5-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine-3-yl]-2,3-dichlorobenzamide of formula (B):

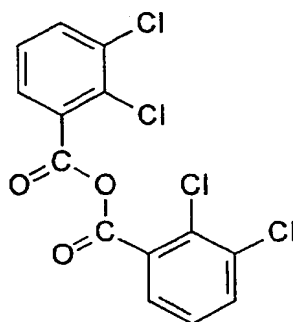
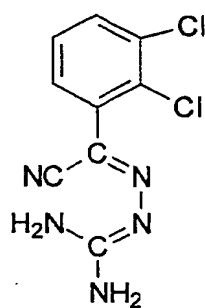


- 25
2. A sample of a compound as claimed in claim 1 which is in substantially pure form.
3. A sample according to claim 2 which has a purity level of 90% or above.
- 30
4. A method of testing the purity of a sample of lamotrigine or a pharmaceutical dosage form comprising lamotrigine, which method comprises assaying the said sample for the presence of N-[5-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine-3-yl]-2,3-dichlorobenzamide.
- 35
5. A method according to claim 4 for testing the purity of a sample of lamotrigine, which includes the steps of:
- (i) dissolving a sample of lamotrigine in a solvent to produce a sample solution;
- (ii) dissolving a sample of N-[5-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine-3-yl]-2,3-dichlorobenzamide in a solvent to produce a reference marker standard solution;
- (iii) subjecting the sample solution and the standard solution to thin layer chromatography to obtain a TLC chromatogram for each; and
- 40
- (iv) estimating the intensity of any secondary spot obtained in the chromatogram of the sample solution, which corresponds in R_f value to the reference marker, against the spot due to the reference marker in the chromatogram of the standard solution.
- 45
6. Use of N-[5-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine-3-yl]-2,3-dichlorobenzamide as a reference marker in testing the purity of a sample of lamotrigine or a pharmaceutical dosage form comprising lamotrigine.
- 50
7. A process for producing a compound as defined in claim 1, which process comprises:
- (i) reacting 2 equivalents of 2,3-dichlorobenzoyl chloride with 1 equivalent of lamotrigine dissolved in pyridine at a temperature of less than 35°C; or
- (ii) cyclising a compound of formula (I):
- 55



in propan-1-ol under reflux.

8. A process according to claim 7 wherein, in step (ii), the compound of formula (I) is produced by reacting together compounds of formulae (II) and (III):

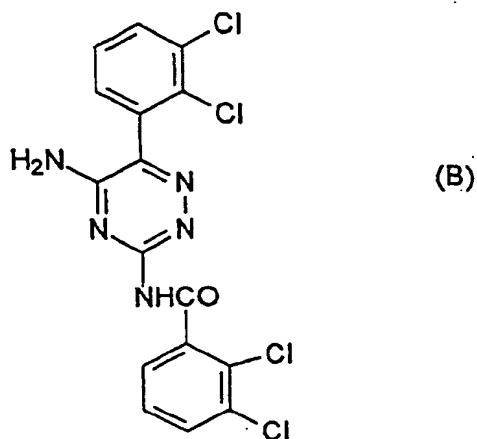


in the presence of a mineral acid.

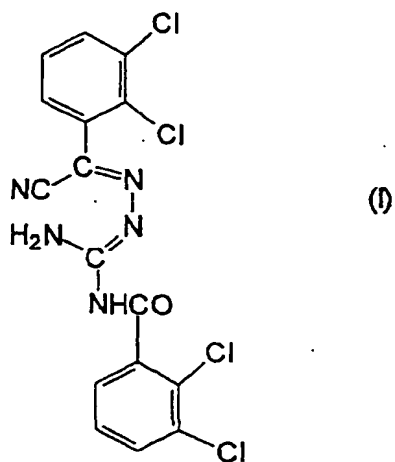
9. A process according to claim 8 wherein the compound of formula (II) is produced by treatment of 2,3-dichlorobenzoyl cyanide with a solution of aminoguanidine bicarbonate in sulphuric acid.

Patentansprüche

1. Verbindung, die N-[5-Amino-6-(2,3-dichlorphenyl)-1,2,4-triazin-3-yl]-2,3-dichlorbenzamid der Formel (B) ist:

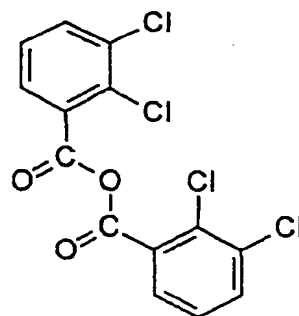
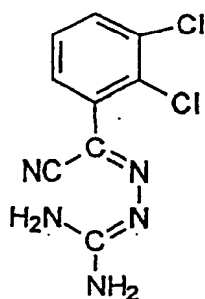


- 20 2. Probe einer Verbindung gemäß Anspruch 1, die in im wesentlichen reiner Form ist.
3. Probe gemäß Anspruch 2, die einen Reinheitsgrad von 90 % oder darüber hat.
- 25 4. Verfahren zur Untersuchung der Reinheit einer Probe von Lamotrigin oder einer Lamotrigin umfassenden pharmazeutischen Arzneiform, wobei das Verfahren die Untersuchung der Probe auf Gegenwart von N-[5-Amino-6-(2,3-dichlorphenyl)-1,2,4-triazin-3-yl]-2,3-dichlorbenzamid umfaßt.
5. Verfahren gemäß Anspruch 4 zur Untersuchung der Reinheit einer Probe von Lamotrigin, welches die folgenden Schritte einschließt:
- 30 (i) Lösen einer Probe von Lamotrigin in einem Lösungsmittel zur Erzeugung einer Probenlösung;
- (ii) Lösen einer Probe von N-[5-Amino-6-(2,3-dichlorphenyl)-1,2,4-triazin-3-yl]-2,3-dichlorbenzamid in einem Lösungsmittel zur Erzeugung einer Referenzmarker-Standardlösung;
- 35 (iii) Unterwerfen der Probenlösung und der Standardlösung der Dünnschichtchromatographie zum Erhalt eines DC-Chromatogramms für jede Lösung; und
- (iv) Abschätzen der Intensität jedes sekundären Flecks, der im Chromatogramm der Probenlösung erhalten wird und der im Rf-Wert dem Referenzmarker entspricht, gegen den Fleck aufgrund des Referenzmarkers im Chromatogramm der Standardlösung.
- 40 6. Verwendung von N-[5-Amino-6-(2,3-dichlorphenyl)-1,2,4-triazin-3-yl]-2,3-dichlorbenzamid als Referenzmarker in der Untersuchung der Reinheit einer Probe von Lamotrigin oder von einer Lamotrigin-umfassenden pharmazeutischen Arzneiform.
- 45 7. Verfahren zur Herstellung einer Verbindung wie in Anspruch 1 definiert, wobei das Verfahren umfaßt:
- (i) Umsetzen von 2 Äquivalenten 2,3-Dichlorbenzoylchlorid mit 1 Äquivalent Lamotrigin, aufgelöst in Pyridin bei einer Temperatur von weniger als 35°C; oder
- 50 (ii) Cyclisieren einer Verbindung der Formel (I):
- 55



in Propan-1-ol im Rückfluß.

8. Verfahren gemäß Anspruch 7, worin in Schritt (ii) die Verbindung der Formel (I) hergestellt wird, indem Verbindungen der Formeln (II) und (III):

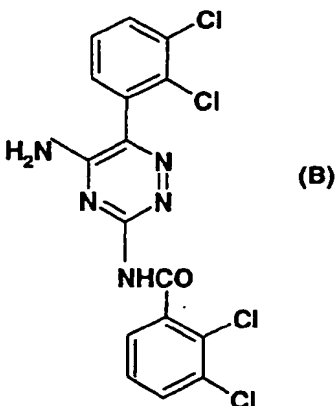


in Gegenwart einer Mineralsäure umgesetzt werden.

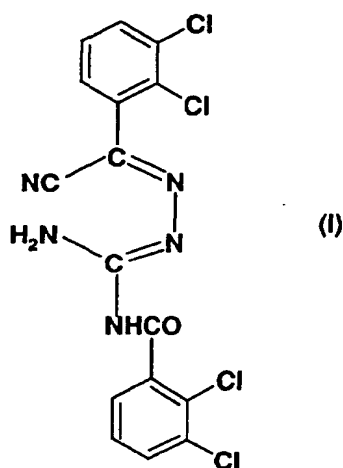
9. Verfahren gemäß Anspruch 8, worin die Verbindung der Formel (II) durch Behandlung von 2,3-Dichlorbenzoylcyanid mit einer Lösung von Aminoguanidinbicarbonat in Schwefelsäure hergestellt wird.

Revendications

1. Composé qui est le N-[5-amino-6-(2,3-dichlorophényl)-1,2,4-triazin-3-yl]-2,3-dichlorobenzamide de formule (B) :

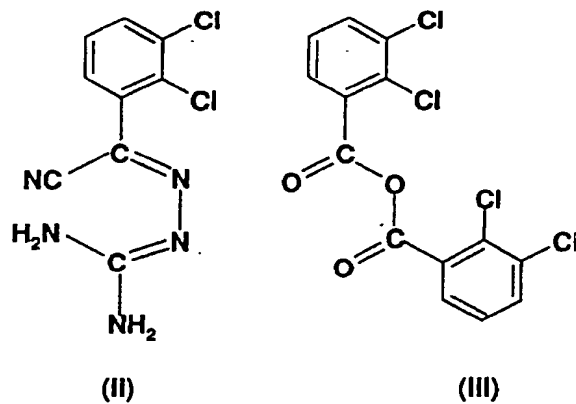


- 20 2. Echantillon d'un composé selon la revendication 1, qui se trouve sous une forme essentiellement pure.
3. Echantillon selon la revendication 2, qui présente un degré de pureté de 90% ou plus.
- 25 4. Procédé de test de la pureté d'un échantillon de lamotrigine ou d'une forme posologique pharmaceutique comprenant la lamotrigine, lequel procédé comprend le dosage procédé consiste à doser dudit échantillon quant à la présence du N-[5-amino-6-(2,3-dichlorophényl)-1,2,4-triazin-3-yl]-2,3-dichlorobenzamide.
5. Procédé selon la revendication 4, pour tester la pureté d'un échantillon de lamotrigine, qui comporte les étapes consistant :
- 30 (i) à dissoudre un échantillon de lamotrigine dans un solvant pour produire une solution échantillon;
 (ii) à dissoudre un échantillon de N-[5-amino-6-(2,3-dichlorophényl)-1,2,4-triazin-3-yl]-2,3-dichlorobenzamide dans un solvant pour produire une solution étalon de marqueur de référence;
 (iii) à soumettre la solution échantillon et la solution étalon à une chromatographie sur couche mince afin d'obtenir un chromatogramme CCM pour chacune d'entre elle; et
 35 (iv) à estimer l'intensité de toute tache secondaire obtenue dans le chromatogramme de la solution échantillon qui correspond en valeur R_f au marqueur de référence, par rapport à celle de la tache due au marqueur de référence dans le chromatogramme de la solution étalon.
- 40 6. Utilisation du N-[5-amino-6-(2,3-dichlorophényl)-1,2,4-triazin-3-yl]-2,3-dichlorobenzamide en tant que marqueur de référence dans le contrôle de la pureté d'un échantillon de lamotrigine ou d'une forme posologique pharmaceutique comprenant la lamotrigine.
7. Procédé de production d'un composé selon la revendication 1, lequel procédé comprend :
- 45 (i) la réaction de deux équivalents de chlorure de 2,3-dichlorobenzoyl avec un équivalent de lamotrigine dissous dans de la pyridine à une température inférieure à 35°C; ou
 (ii) la cyclisation d'un composé de formule (I)
- 50
- 55



20 dans du propan-1-ol à reflux.

8. Procédé selon la revendication 7 dans lequel, dans l'étape (ii), le composé de formule (I) est produit en faisant réagir ensemble les composés de formules (II) et (III):



en présence d'un acide minéral.

9. Procédé selon la revendication 8 dans lequel le composé de formule (II) est produit en traitant le cyanure de 2,3-dichlorobenzoyl par une solution de bicarbonate d'aminoguanidine dans de l'acide sulfurique.